Epilepsy in glioma patients:

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SUMMARY

general discussion and future directions

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The main objective of this thesis was to contribute to a more tailored management of epilepsy in glioma patients, by focusing on two major aspects: 1) the effect of antitumor treatment on epilepsy and its clinical significance, and 2) the epidemiology and treatment of epilepsy in the end of life (EOL) phase. In this chapter an overview is provided of our most important findings, as well as the methodological considerations and directions for future research.

Antitumor treatment and seizure outcome

Radiotherapy and chemotherapy play an important role in achieving seizure control in glioma patients with epilepsy. In **chapter 2**, we showed that both treatment modalities frequently lead to a reduction in seizure frequency, or even prolonged seizure freedom. However, most studies are small retrospective patient series that lack an appropriate control group. In studies of relatively high quality and with the larger patient numbers, a seizure reduction between 44% and 77% was observed. Seizure control implies an important clinical benefit for the patient.[1;2] In patients with low-grade glioma (LGG), the presence of epilepsy as well as the inability to achieve complete seizure control are associated with a lower health-related quality of life (HRQOL).[3;4] Apart from oral antiepileptic drugs (AEDs), antitumor treatment is therefore a cornerstone in the management of epilepsy in glioma patients.

In our cohort of LGG patients we observed a ≥50% reduction in seizure frequency after treatment with temozolomide (TMZ) in 44% of cases, which was in line with previous studies. More importantly, a ≥50% seizure reduction appeared to be a consistent prognostic marker for progression-free survival and overall survival, as described in **chapters 3 and 4**. In other words, LGG patients who develop a significant seizure reduction at 6, 12 and months after initiation of TMZ treatment generally have a better survival compared to those without a seizure reduction. These findings are of major clinical significance, since the radiological assessment of response in LGG patients faces numerous barriers. First, establishing changes in tumor size on subsequent MRI's is difficult. The assessment of tumor size is done through linear measurements and is subject to inter- and intra-individual variation, because defined boundaries are lacking in most gliomas due to their irregular, infiltrative growth pattern.[5] Second, in HGGs tumor response can frequently be measured by a decrease in enhancement, whereas LGGs are often non-contrast-enhancing tumors. As a result, response assessment in LGGs depends on T2 or fluid attenuated inversion recovery (FLAIR) images that are less sensitive to detect tumor response or progression.[6] Third, objective radiological responses in LGGs are often delayed or even lacking after antitumor treatment.[7] Although radiological responses seem to occur more often in

patients who show a clinical improvement, we found that after TMZ treatment 21-50% of LGG patients with stable disease on MRI did experience a seizure reduction.[8-10] Considering the association between survival and improved seizure outcome after antitumor treatment even before or in absence of an objective radiological response, seizure reduction could serve as an early marker of tumor response.

It is important to note that in glioma patients a low prevalence of seizures is not necessarily associated with a better survival. Instead, because seizure prevalence is inversely related to the growth rate of the tumor, the highest prevalence of seizures are found in slow-growing tumors, such as diffuse LGGs and glioneuronal tumors.[11-13] As a result, seizures may be seen as a favorable prognostic factor for survival.[14;15] Although an increase in seizure frequency is often related to tumor progression, studies on seizure recurrence after successful tumor resection have shown that the association between an increased seizure frequency and tumor recurrence is controversial.[16;17] In addition, seizures sometimes occur as an acute, but temporary complication of resection or radiotherapy, without having a relation with patient's prognosis.[18] Thus, during or shortly after treatment with TMZ, a seizure reduction might be interpreted as a positive prognostic sign, however, this observation cannot be extrapolated to the general course of the disease.

The complex association between seizure occurrence or a changing seizure frequency on the one hand, and survival on the other hand is indicative of the multiple mechanisms that are involved in tumor-related epilepsy. Gradual functional changes of the cerebral tissue are thought to underlie the high epileptogenicity of LGG.[19] In HGG, abrupt tissue damage of the tumor itself together with an infiltrative growth pattern and peritumoral ischemia resulting in excitability are possible pathophysiological mechanisms.[20;21] After tumor resection, seizure reduction may be related to the beneficial effect of surgery on tumor progression.[16] However, the precise mechanisms that lead to a seizure reduction after tumor-directed treatment remain largely unknown. Previous studies showed that a seizure reduction may take place a few weeks or even days after the initiation of antitumor treatment.[22;23] Therefore, it can be hypothesized that acute structural changes within the tumor and its microenvironment play a role in the reduction of seizures, rather than the slow functional changes that are thought to be related to the epileptogenicity of LGGs. The fact that seizure frequency also diminishes in the absence of a response on MRI at least suggests that a seizure reduction is not merely caused by a significant reduction in tumor size.

Apart from the pathophysiological mechanisms underlying seizure reduction after antitumor treatment, other questions remain unsolved. First, based on the current literature, it is unclear whether radiotherapy or chemotherapy is superior in reducing seizures in glioma patients. This question might be answered by secondary analyses of the results of the European Organization for Research and Treatment of Cancer (EORTC) phase 3 trial 22033-26033, comparing postoperative TMZ and irradiation in WHO grade II glioma patients. Moreover, the prognostic value of a seizure reduction after radiotherapy has not yet been sorted out. Nonetheless, our findings suggest that seizure reduction is a valuable clinical parameter in evaluating tumor response in patients with LGG who are treated with TMZ. New studies should be initiated to validate seizure reduction as a surrogate marker for tumor response, as well as to include other clinical measures in addition to radiological assessment.

AED withdrawal after antitumor treatment

Antitumor treatment frequently leads to seizure freedom for a longer period following particularly surgical resection[24-27], but also for TMZ chemotherapy and radiotherapy.[28-30] AEDs are generally discontinued some time after successful epilepsy surgery in patients with non-tumor-related epilepsy, but in glioma patients there is limited information on AED tapering and withdrawal.[31;32] Therefore, we initiated a prospective observational study on AED management in glioma patients with long-term seizure freedom, as presented in **chapter 5**. As the study is primarily aimed at exploring the willingness and feasibility to withdraw AEDs in glioma patients, both patients who prefer AED withdrawal and patients who prefer continuation are followed after the patient and the physician have made a shared decision.

In patients with ongoing disease stability seizures are less likely to recur, which means that patients who withdraw their AEDs are no longer exposed to the side effects of AEDs. By withdrawing AEDs, long-term toxicity, drug-drug interactions, cognitive side effects, as well as teratogenicity can be avoided.[33-35] Nonetheless, the benefits of AED withdrawal need to be weighed against the risk of seizure recurrence. Unlike patients with non-tumor related epilepsy, glioma patients are always at risk of developing tumor progression, which might induce seizure relapse. Therefore, AED withdrawal might particularly be valuable in patients who experience prolonged seizure freedom after successful antitumor treatment, and have a favorable prognosis. This particularly applies to patients with LGG and anaplastic glioma, who regularly show long-term disease stability. Within this subgroup of glioma patients, patients with favorable prognostic factors, such as presence of chromosome 1p and 19q co-deletion or IDH1 mutation, histopathological diagnosis of an oligodendroglioma, younger age and a macroscopically complete resection might particularly benefit from AED withdrawal.[36]

The non-randomized study design should contribute to a more individually tailored management of AED treatment in glioma patients. Preliminary results show that the vast majority of patients participating in our study are indeed willing to withdraw their AEDs, even in the absence of adverse drug effects. A complete analysis of this observational study will indicate which arguments are of crucial importance in the decision to either withdraw or continue AED treatment. Eventually, this study may lower patient's and physician's threshold to withdraw AEDs and could guide future recommendations concerning optimal AED treatment in glioma patients.

Symptom management in the EOL phase

During the EOL phase of glioma patients, antitumor treatment is no longer meaningful, and relief of suffering and achieving symptom control becomes the primary goal of treatment. The EOL phase may start days, weeks or even months before death, but is generally confined to the last three months of life. In general, symptom burden in glioma patients becomes very high, particularly shortly before death. Symptoms such as seizures, cognitive disturbances and drowsiness are prominent, and interfere with patient's ability to participate in EOL decision-making.[37;38] Neurological deficits, such as paresis, and cognitive decline disturb patient's HRQOL, and cause a huge burden on caregivers.[39-41]

In **chapter 6** we observed the importance of effective symptom treatment in the EOL phase of glioma patients. Besides the information provided by the physician, the place of death and the efficacy of symptom treatment were markers for good quality of care as perceived by the patient. Patients in The Netherlands, Scotland and Austria were equally satisfied with the quality of EOL care. However, to further improve quality of care, one has to take into account the different health care systems in these countries, as well as the cultural differences in patient's preferences and experiences with EOL care. Our analysis underscored patient's preference to receive EOL care at home. Previous studies showed that the absence of transitions between health care settings also contributes to a dignified death.[42;43] In order to avoid rehospitalization of patients in the EOL phase, medication that reduces symptom burden should be easily applicable in an out-of-hospital setting.[44]

The various symptoms that affect glioma patients in the EOL phase are outlined in **chapter 7**. In line with previous studies, we found that disease-specific EOL symptoms are the main concern in glioma patients. Of all EOL symptoms, loss of consciousness and dysphagia remarkably increased towards death. Difficulties with swallowing, whether or not induced by an impaired consciousness, apraxia or muscle weakness, have previously been reported in up to 85% of glioma patients in the last days before death.[45] The inability to swallow most probably explains the discontinuation of AEDs and corticosteroids that we found in 21% and 25% of glioma patients, respectively. The presence of a causal relationship between disease-specific symptoms and drug withdrawal, however, still needs to be determined.

Epilepsy in the EOL phase: epidemiology and management

Chapters 8 and chapter 9 show that seizures are one of the main concerns in the EOL phase of glioma patients. In our retrospective cohort study, we found that seizures affect 29% of HGG patients in the last week before death, which is in line with previous reports on glioma patients[46-48], and is clearly higher than for patients with brain metastases.[49;50] Uncontrolled seizures may not only result in higher morbidity, but also cause additional stress for patient's caregivers, who already experience a heavy burden of care.[40;51;52]

Apart from status epilepticus, we found no specific risk factors for the occurrence of seizures in our cohort of HGG patients. However, it is important to stress that seizures in the EOL phase can affect both patients with and without a history of epilepsy. Of all HGG patients with epilepsy in the EOL phase, we found that 22% had de novo seizures. This suggests that other factors contribute to the occurrence of seizures during the EOL phase than during earlier disease phases. The development of necrosis and edema, for example, as well as rapid tumor infiltration of the peritumoral environment may lead to excitability.[21] Organ dysfunction resulting in electrolyte imbalances may also induce acute symptomatic seizures.[53] Seizure threshold could be further lowered by the concomitant use of antipsychotics, such as clozapine, or tricyclic antidepressants.[54-56] In patients who are already on AEDs, other EOL symptoms may interfere with the regular oral administration of AEDs, which sooner or later could contribute to inadequate serum AED levels. The latter issue in particular makes adequate seizure management in the EOL phase often difficult.

Considering the high frequency of impaired consciousness and dysphagia in the EOL phase hampering oral drug administration, together with a substantial risk of developing seizures, we started a feasibility study using non-oral AEDs in patients with a history of epilepsy. In **chapter 10** we demonstrated that swallowing difficulties are indeed a major problem in the EOL phase, but in most cases develop no earlier than one week before death. In some cases, we found that a rapid progressive deterioration and death prevented the start of non-oral AED administration. Thus, the inability to swallow oral AEDs generally seems to affect glioma patients only in a very advanced stage. Given the high participation rate and caregiver's satisfaction, the use of alternative AED administration routes clearly responds to a need of glioma

patients with epilepsy. Our findings therefore support that refraining from AED treatment in the EOL phase is undesirable in those glioma patients who have a history of epilepsy. However, it remains unclear whether alternative administration routes really contribute to increased seizure control in the EOL phase. Moreover, if we could identify risk factors for the occurrence of seizures, other than a history of epilepsy or status epilepticus, more specific preventive treatment protocols could be developed.[57]

DISCUSSION

Epilepsy and antitumor treatment

Evaluating seizure outcome involves methodological challenges, particularly in case of a retrospective study design, such as we used in chapter 3 and chapter 4, and which is present in most studies on seizure outcome after antitumor treatment as we have shown in our systematic review in chapter 2. Seizure frequencies, usually based on self-reported diaries, are patient-reported outcomes, which are prone to various problems. Patient's limited awareness of seizures is one of the fundamental issues. Previous studies suggest that 23-61% of patients with epilepsy fail to recognize seizures.[58;59] Possibly, in the glioma population these percentages are even higher, given the cognitive impairments or impaired consciousness additionally affecting seizure awareness. Although informal caregivers may recognize seizures more accurately, they will also miss seizures as they are not continuously in proximity to the patient.[60] Patients might also record other events as seizures. Moreover, lack of compliance in recording seizures, delayed completion of a seizure diary or losing a paper diary may affect the observed seizure outcome.[60] Apart from a recall bias caused by the patient or their caregivers, reporting bias due to the physician's potential inaccuracy in recording patient's seizure status may have affected the outcome in our studies as well.

Several other forms of bias could also have influenced the results. There might be a selection bias towards patients with unresectable tumors in both of our retrospective studies on seizure outcome after TMZ (chapters 3 and 4), as we included a relatively large group of patients who had only undergone a biopsy. Furthermore, although we restricted our analyses to LGG patients on a stable AED dose in both studies to rule out an effect of AED treatment on seizure outcome, other antitumor treatments, such as previous surgery or radiotherapy, might have influenced seizure outcome. Publication bias could have played a role in our systematic review on seizure outcome after antitumor treatment, due to a possible tendency to report the positive effects of antitumor treatment. Therefore, our findings as described in chapter 2 may overestimate the true effect of antitumor treatment on epilepsy.

In the studies described in chapters 3 and 4, seizure reduction was one of the primary outcome measures. Apart from the difficulties with analyzing seizure frequencies, the question emerges whether a ≥50% seizure reduction means a clinical significant benefit for the patient. In a study evaluating the association between seizure reduction and HRQOL, no measurable impact on HRQOL was observed in patients with non-tumor related epilepsy who had a ≥50% seizure reduction. Patients who reported complete seizure freedom, however, showed significantly better scores on HRQOL subscales compared to patients without seizure freedom.[61] Another study demonstrated that HRQOL is lower in patients with temporal lobe epilepsy who experience a <90% seizure reduction after surgery or AED treatment compared to patients who have a ≥90% seizure reduction or seizure freedom.[62] Apparently, only complete seizure freedom leads to a clinically meaningful improvement in terms of HRQOL in these patients, which puts the universally applied threshold of a ≥50% seizure reduction in seizure frequency in a different light. Although the association between HRQOL and seizure reduction rate is unknown in glioma patients, these findings at least demonstrate that seizure outcome measures should be chosen carefully and preferably should be used in combination with other clinical outcome measures, including HRQOL.

Epilepsy as a major symptom in the end of life phase

In EOL research, retrospective study designs such as we used in chapters 6, 7 and 8 are well-accepted and even have several advantages over prospective study designs. Patients are easily identified, and selection bias is reduced when selecting patients after they have died.[63] In prospective EOL studies, physicians need to recognize when patients approach the EOL phase and should be prepared to discuss study participation with a patient whose condition is declining. This may induce a significant risk of selection bias. Another option is to prospectively follow a cohort including all patients diagnosed with HGG until death. Although generating the best evidence, this latter type of research would be very demanding for both patients and physicians.[57]

However, retrospective EOL studies obviously also have their limitations. Recall bias may have influenced our findings, given the large interval between patient's death and the completion of the questionnaire. There is some selection bias towards patients with a shorter overall survival, as deceased patients were selected from a cohort of HGG patients diagnosed within a specific period of time. In addition, the studies described in chapters 6 and 7 partly depend on information derived from the relatives' questionnaire. Although proxy ratings are essential in retrospective EOL research, the agreement between patient and patient-by-proxy ratings is debatable.[64-66] Patient's cognitive disturbances or somnolence may interfere with

communication. As a consequence, relatives are not always aware of some aspects of the patient's situation. Moreover, relatives may answer according to their own perspective, or might give socially desirable responses. Nonetheless, as a result of the retrospective study design and the availability of proxy ratings we were able to collect a substantial amount of data on the EOL phase of glioma patients. Furthermore, the identical study design that we used in the different countries allowed us to make a unique comparison of EOL care for glioma patients throughout Europe.

FUTURE DIRECTIONS

The first part of this thesis has focused on the clinical significance of antitumor treatment on epilepsy. Apart from tumor resection, radiotherapy and chemotherapy appear to contribute to seizure control in a substantial part of glioma patients. Furthermore, seizure reduction after chemotherapy with TMZ counts as a favorable prognostic factor for both progression-free and overall survival in patients with LGG. These findings are of high clinical relevance. In fact, when patients report an evident reduction in seizure frequency in the first months after initiation of TMZ, this could be regarded as an early sign that the tumor responds to treatment even in absence of a measurable response on MRI. In most cases, the patients we analyzed had previously undergone different antitumor treatments. In order to validate our findings with regard to the effect of TMZ on seizure outcome, future studies should focus on a more homogeneous population of LGG patients, who for example receive TMZ as the first antineoplastic treatment. Similar studies are needed in patients who receive radiotherapy. Recently, a response assessment in neuro-oncology (RANO) working group has been started to discuss the value of assessment of seizures in clinical trials. Seizure outcome measures not only need to play a more prominent role in future trials, but their value in relation to radiological response assessment should be further explored. Preferably, they are implemented in clinical trials together with other clinical outcome measures, such as symptom burden, neurocognitive functioning and HRQOL. In this way a comprehensive view of tumor response could be developed, which reflects the effect of treatment as much as possible.

The prospective observational study on AED withdrawal in glioma patients with long-term seizure freedom should eventually contribute to a more tailored AED management. In case AED withdrawal indeed appears to be safe and feasible, it may prevent unnecessary use of AEDs and reduce the risk of adverse drug effects in glioma patients with long-term stable disease. To further optimize AED management during the course of the disease, new insights into the timing of AED withdrawal and the relation between tumor progression and seizure recurrence are needed. Ideally, in LGG patients seizure frequencies should be closely monitored from the time of diagnosis until death. This might help to shed light on the complex relation between seizure occurrence, tumor behavior and survival. In this context, the development of a standardized seizure diary, that is of value for both clinical practice and research purposes, is crucial to further improve the reliability of seizure outcome measures.

In the second part of this thesis we have demonstrated that epilepsy is one of the major issues in the EOL phase. However, in most patients the management of seizures is particularly difficult during the last days before death, when symptoms such as an impaired consciousness or swallowing difficulties become inevitable, and hamper seizure treatment. To develop more tailored treatment guidelines, future studies should aim at identifying risk factors for seizures in the EOL phase. Given the risk of seizures in the EOL phase and the feasibility of administering non-oral AEDs in case of swallowing difficulties, we believe that physicians should strive to continue AED treatment until death in glioma patients with epilepsy. Therefore, randomized controlled trials should aim at comparing the efficacy of different types of non-oral AEDs in terms of seizure outcome.

In general, the reduction of symptom distress has to be one of the main goals of EOL care, as it may contribute to further improvements in the perceived quality of care. To avoid re-hospitalization or unnecessary transitions during the EOL phase, EOL care should be aimed at providing symptomatic treatment in an out-of-hospital setting, such as at home or in a hospice. Therefore, future EOL studies should include interventions that can easily be applied by the patient or informal caregivers. In order to deliver the best care during the EOL phase, the value of timely discussing patient's preferences within the context of the particular health care system needs to be evaluated. Eventually, this should lead to the development of widely applicable treatment guidelines for the EOL phase of glioma patients.

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